Diamond-Blackfan Anemia 101

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DBA Camp, July 22, 2013
When You Hear ...., Think ...., Or ....
Some Things are Clear; Some are Not
Diamond-Blackfan Anemia

DBA, not BDA
Diamond and Blackfan

Louis K Diamond, 1902-1999  Kenneth D Blackfan 1883-1941
First DBA Scientific Meeting, Bellagio, Italy
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Hematology</th>
<th>Leukemia</th>
<th>Solid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi Anemia (FA)</td>
<td>Aplastic</td>
<td>AML</td>
<td>SCC</td>
</tr>
<tr>
<td>Dyskeratosis Congenita (DC)</td>
<td>Aplastic</td>
<td>AML</td>
<td>SCC</td>
</tr>
<tr>
<td>Diamond-Blackfan Anemia (DBA)</td>
<td>Pure anemia</td>
<td>AML</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>Shwachman-Diamond Syndrome (SDS)</td>
<td>Neutropenia</td>
<td>AML</td>
<td>-</td>
</tr>
<tr>
<td>Severe Congenital Neutropenia (SCN)</td>
<td>Neutropenia</td>
<td>AML</td>
<td>-</td>
</tr>
<tr>
<td>Amegakaryocytic Thrombocytopenia</td>
<td>Thrombocytopenia</td>
<td>AML</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia Absent Radii (TAR)</td>
<td>Thrombocytopenia</td>
<td>AML</td>
<td>-</td>
</tr>
</tbody>
</table>

These disorders are the “Inherited Bone Marrow Failure Syndromes” (IBMFS).
IBMFS Pathways

- DNA Repair: FA
- Telomere biology: DC
- Ribosomes: DBA, SDS, DC
- Platelet production: Amega
- Apoptosis: SCN, others
DBA in Australia
Background

- Diamond-Blackfan anemia (DBA), an Inherited Bone Marrow Failure Syndrome (IBMFS) with varying degrees of pure red cell aplasia
- Heterogeneous disorder
- Patients with an IBMFS have an increased risk of cancer (leukemia and solid tumors)
- Correlation between physical and/or laboratory features and outcomes?
- Birth rate 5-10 per million live births
First Publications

- **Josephs HW**: Anaemia of infancy and early childhood. Medicine, 1936
- **Diamond LK, Blackfan KD**: Hypoplastic anemia. Am J Dis Child, 1938
- Why not “Josephs, Diamond, Blackfan anemia”? 
Diamond-Blackfan Anemia

- Normochromic, usually macrocytic anemia, developing in infancy
- Reticulocytopenia
- Marrow erythroblastopenia
- Normal or slightly decreased leukocytes
- Normal or increased platelets
- Increased fetal hemoglobin (Hb F)
- Increased red cell adenosine deaminase (ADA)
- ~25% with physical findings: short, abnormal thumbs, etc
Supportive Criteria for DBA

- Major
  - Mutation in a DBA gene (ribosomal?)
  - Family history of DBA

- Minor
  - Increased red cell ADA
  - Typical physical abnormalities
  - Increased fetal hemoglobin (% Hb F)
  - Other IBMFS ruled out

Vlachos et al, Br J Haematol 2008
Method

- Literature review
- Prospective cohort at the NCI

Biases:
- Volunteerism
- Selection (publication, enrollment)
- Information (incomplete records, self-report)
- Survival
DBA Literature 1936-

- Case Reports: ~1250; (+ Case Series >1100)
- Male:Female: 1.05:1
- Died: 141 (11% crude rate)
- Alive: median age 7 yrs (0-60)
- Died: median age 9 yrs (0-65)
- Abnormal physical findings 30%
- Remissions reported 10%

*Biased by under-reporting, over-reporting, and missing data.*
Median age at diagnosis 2.5 mo; 85% by 1 and 97% by 5 years

Shimamura and Alter, Blood Reviews 2010
Survival Before and After 2000

More than 83% were over age 18
Aase Syndrome and other Thumbs
Neck
DBA Literature Physical Abnormalities

- Any PE: 30%
- Short: 15%
- Thumbs + Hands: 15%
- Head, face, palate: 10%
- Other: 5%
- Low BW: 5%
- Cardiac: 5%
- Eyes: 5%
- Skeletal: 5%
- GU: 5%
- Gonads: 2%
- Neck: 2%
- Devt: 2%
- Ears: 2%
- CNS: 1%
Comparison of Physical Findings

Note that NCI has higher frequencies – more thorough exams?
Major Complications in DBA

- Anemia
- Rarely pancytopenia
- Iron overload
- MDS/AML
- Sarcoma
Treatment of DBA

- Current:
  - Steroids
  - Transfusions
  - Iron chelation
  - Stem cell transplant

- Future clinical trials:
  - Leucine
  - Lenalidomide

- Spontaneous remission, ~25%
Steroids

- Prednisone, 2mg/kg/day, divided 3 times per day, for 1-4 mo
- If response, taper slowly
  - 2 doses per day x 1 month
  - 1 dose per day x 1 month
  - Double this dose, every other day in am
- If no response, transfuse
- Consider stem cell transplant (SCT)
Transfusions

- At diagnosis
- For first year of life – or not?
- Hb drops by ~1 gm/week
- Transfuse every 4 weeks, with 15 mL/kg
- Pre-tx, Hb <8 g/dL
- Post-tx, Hb >12 g/dL
Iron Chelation

- Generally after 15-20 transfusions
- Age >2 years
- Ferritin >1000
- Cardiac and liver iron measured by MRI
- Desferal: subQ or IV, 40-50 mg/kg/day, over 8-12 hrs (overnight)
- Exjade (oral)
Stem Cell Transplant

- **Who?**
  - Steroid-refractory, transfusion-dependent
  - Age <10?

- **What?**
  - Bone marrow
  - Cord blood
  - Peripheral blood (stimulated with G-CSF)

- **Donors?**
  - Matched sibling
  - Unrelated
  - Haploidentical
  - Cord
Stem Cell Transplant by Dates

Better survival in recent interval, but small numbers
Literature Cases: Cumulative Probability of Cancer by Age 50 yrs

No. of Cases in Reports, with or without Cancer

We need better qualitative and quantitative data.

Shimamura and Alter: Blood Reviews 2010
### NCI IBMFS, since 2002

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Families</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi Anemia</td>
<td>92</td>
<td>112</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>92</td>
<td>139</td>
</tr>
<tr>
<td><strong>Diamond-Blackfan Anemia</strong></td>
<td>68</td>
<td>97</td>
</tr>
<tr>
<td>Shwachman-Diamond Syndrome</td>
<td>38</td>
<td>44</td>
</tr>
</tbody>
</table>

Numbers include “XX-like”, i.e. patients who do not quite meet criteria for a syndrome but may after molecular testing is completed.
Genetics
Ribosome Genes

Courtesy of S Savage
DBA Inheritance

- Autosomal dominant
- 40s ribosome biogenesis
  - \textit{RPS19}
  - \textit{RPS26}
  - \textit{RPS10}
  - \textit{RPS24}
  - \textit{RPS17}
  - \textit{RPS7}
  - \textit{New, NCI}
- Haploinsufficiency, 12 genes
- 60s ribosome biogenesis
  - \textit{RPL5}
  - \textit{RPL11}
  - \textit{RPL35a}
  - \textit{RPL26}
  - \textit{New, Gazda}
  - \textit{GATA1} (X-linked)
Ribosomal Genes: NCI Cohort and Literature

Unknown: 55%

43%

45%
Disease-Associated Mutations

A mutation is a change in the normal base pair sequence.

Commonly used to define DNA sequence changes that alter protein function.
Exome Sequencing and Filtering

http://www.nature.com/ng/journal/v42/n1/images/ng0110-13-F1.jpg
DBA: New Gene, Exome Data

- Autosomal Dominant
- Exclude the following variants:
  - synonymous
  - minor allele frequency >5%
  - >2 times in internal control population
  - >3 times in ESP
  - segmental duplications >2
  - do not appear in the proband

14q21.3
Nonsynonymous amino acid change
Predicted to be deleterious
...Polyphen-2, CONDEL, SIFT, MuPro, I-Mutant
RPS29
Zebrafish rps29 Mutant has a late-stage Erythropoietic Defect

# Red Cell Adenosine Deaminase (ADA)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glader, 1983</td>
<td>12/12</td>
<td>100</td>
</tr>
<tr>
<td>Whitehouse, 1986</td>
<td>9/19</td>
<td>47</td>
</tr>
<tr>
<td>Glader, 1986</td>
<td>23/26</td>
<td>88</td>
</tr>
<tr>
<td>Glader, 1988</td>
<td>26/29</td>
<td>90</td>
</tr>
<tr>
<td>Orfali, 2004</td>
<td>48/50</td>
<td>96</td>
</tr>
<tr>
<td>Willig, 1998</td>
<td>28/34</td>
<td>82</td>
</tr>
<tr>
<td>Fargo, 2012</td>
<td>31/37</td>
<td>84</td>
</tr>
</tbody>
</table>

Fargo *et al*, Br J Haematol 2013
ADA in DBA, non-DBA, and Relatives

Figure 1

ADA is ~85% sensitive, and >90% specific

Fargo et al, BJH 2013
ADA and DBA Gene Mutation

ADA is not always elevated (arrow) in DBA, and elevated ADA does not always track with mutated DBA gene

Fargo et al, BJH 2013
Telomeres <1% of normal are diagnostic of dyskeratosis congenita, and are very RARE in DBA.

Alter et al, Blood 2007
NCI DBA Cancer

- Colon 1
- Lung 2
- Skin basal cell 1
- MDS/AML 0

Numbers too small to be significant

Alter et al, BJH 2010
Risk for Cancer in FA, DC and DBA, NCI Cohort

*Not significant in DBA

Alter et al, BJH 2010
Cancer in the DBAR, 17/608 Patients

Significant types of cancers

Vlachos et al: Blood 2012
DBA compared with FA, DC, SDS

Overall Survival

Survival Free of Cancer

Survival Free of BMF

Alter et al, BJH, 2010
NCI DBA Data Summary

- Physical anomalies and/or short stature are common.
- More frequent than previously reported:
  - Head and face, cardiac, skeletal (other than upper limb) and developmental delay.
- Transfusions and steroids are associated with long-term morbidity.
- Cancer in 3%.
- Survival plateau 80% at 35 yrs.
Inherited bone marrow failure syndromes (IBMF) are rare disorders in which there is usually some form of aplastic anemia (failure of the bone marrow to produce blood), associated with a family history of the same disorder. Some of these conditions have typical changes in physical appearance or in laboratory findings which suggest a specific diagnosis. There are several well-described syndromes, which can be recognized by health care experts. There are also patients who are harder to classify, but who appear to belong in this category.

Patients with these syndromes have a very high risk of development of cancer (either leukemia or certain solid tumors). At the moment we cannot predict which specific patient with an IBMFS is going to develop cancer. The NCI EMFS Contact Study will enroll North American families in which at least one member has or had an IBMFS. We plan to:

- include individuals known to have an IBMFS as well as their first degree relatives (brothers, sisters, parents, and children);
- collect clinical information from study participants and their physicians;
- perform detailed physical examinations, x-rays and routine laboratory tests on those who are interested in traveling to the NIH to be seen in person by our team;
- attempt (on a research basis) identification of the specific genetic mutation that is associated with each family’s disease;
- screen participants for early changes related to the specific cancer that occur in each syndrome;
- perform detailed research laboratory studies on blood and tumors collected from study participants, in an effort to understand the process by which cancers develop;
- monitor study participants in an ongoing fashion to determine the rate at which complications develop related to each disease, and to identify those complications more precisely;
- provide suggestions to study participants and their physicians regarding how to best take care of family members who are affected with a particular IBMFS, and;
- offer genetic counseling, and an opportunity to learn the results of mutation testing, for those persons who decide that this information will be of use to them.

The Principal Investigator responsible for this study is Blanche P. Albr, MD, MPH. For further information regarding her credentials and experience, please see: http://cancer.gov/nciclinicaltrials/Aler.html.

Our overall goal is to reach a better understanding of how cancers develop in persons with IBMFS, so that we may improve the health care which can be offered to persons with these disorders.